Allergy Abstracts

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From the Allergy Division of
The Jewish Hospital of Brooklyn

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Asthma and Hay Fever

Controlled Trial of Effects of Cortisone Acetate in Chronic Asthma. Report to the Medical Research Council by the Subcommittee on Clinical Trials in Asthma. Lancet **2**: 798. 1956.

Patients with severe bronchial asthma without complicating bronchopulmonary infection were studied in the outpatient clinics of six different hospitals. The subjects ranged in age from 14 to 60 years. Only those patients who had asthma of at least three months' duration and who had not had a remission for longer than two weeks during the three months immediately preceding the study were selected. Of 96 patients in the study group, 49 were treated with cortisone and 47 served as controls. A double blind test was followed, as far as medication was concerned, neither the patient nor the doctor being aware of the true contents of the preparations used. This was effected by the use of placebos containing starch and lactose with traces of

quinine hydrochloride and magnesium stearate made up to be indistinguishable, on the basis of size, color, shape, and taste, from the cortisone preparations.

Patients were observed for 6 months while they were receiving medication and for 3 months after the medication had been discontinued. A standard dosage schedule was adopted and consisted of 300 mg. of cortisone acetate for the first 24 hours, 200 mg. on the second and third days, and then 100 mg. daily for the next 4 days. After the first week, all dosage schedules were left to the discretion of the attending physicians, patients in the control groups receiving equivalent doses of placebo preparations. Patients in both groups were permitted to continue the use of antispasmodic medication as needed during the trial period.

The cortisone-treated patients appeared substantially improved at first when compared with the controls. As the study progressed, however, the difference between the two groups diminished. This was clearly demonstrated by the capacity of the control group to engage in as much activity as the cortisone-treated group. During the follow-up period, it was almost as difficult to wean patients from the placebo as it was to wean them from the steroid. The results observed at the end of the follow-up period were essentially the same as those seen during the first 6 months of the study.

Ten patients in the control group failed to complete the study. In 5 cases severe status asthmaticus necessitated additional treatment, while the other 5 stopped the medication of their own volition. In 9 of the hormone group, treatment was interrupted for various reasons, some because of complications (perforated ulcer or psychiatric disturbance), others because of intractable asthma, and some of their own volition. As a final evaluation, the authors conclude that the patients continuously treated for 6 months with cortisone showed no greater improvement than did those patients in the control group.

R. W.

Controlled Trial of Effects of Cortisone Acetate in Status Asthmaticus. Report to the Medical Research Council by the Subcommittee on Clinical Trials in Asthma. Lancet **2**: 803, 1956.

The treatment of status asthmaticus with cortisone acetate was evaluated in 13 different hospitals. Thirty-two patients, 14 years of age and over, who had had at least one severe attack of asthma were studied. None of the patients had ever previously received cortisone. All of the asthmatics in the study group had been hospitalized for 24 hours and had not been benefited by routine hospital therapy for status asthmaticus, including subcutaneous Adrenalin 1:1,000, intravenous aminophylline, Isuprel inhalations, oxygen, antibiotics, and sedatives. There were 15 patients in the cortisone-treated group and 17 patients in the control group. The placebo tablets were indistinguishable from the cortisone tablets and neither the patient nor the doctor knew which medication was being dispensed.

During the first 24 hours each patient in the test group was given 300 mg. of cortisone acetate by mouth in divided doses. On subsequent days the dosage was gradually reduced, so that by the sixth day each patient was receiving 100 mg. and by the tenth day the treatment was discontinued. Patients in both groups were also maintained on symptomatic treatment with the exact directions being left to the discretion of the physician in charge.

There was more rapid improvement in the patients treated with cortisone than in the control patients. At the end of the fourth day, 10 of the 15 in the hormone-treated group were markedly relieved, while only 4 of the 17 in the control group were similarly affected. At the end of the two-week period

of observation, 11 of the 15 in the cortisone group were free of asthma but only 4 of the 17 control patients felt equally well. Follow-up studies on the patients three months after treatment showed that both groups tended to have a high percentage of relapses. Status asthmaticus recurred in 9 of 11 patients in the cortisone-treated group and in 7 of 14 in the control group. One patient in the cortisone group died during the study, apparently from overwhelming infection. All 5 patients in the control group, who had to be taken out of the study because of the seriousness of their condition, responded well to ACTH therapy. The authors state that routine therapy is usually successful in relieving status asthmaticus, but when such treatment fails the addition of cortisone to the treatment program will usually produce beneficial results quickly. R. W.

Antibody-Like Factor in Serums of Ragweed-Sensitive Individuals Shown in Vitro. Sehon, A. H., Gordon, J., and Rose, B.: Science **125**: 597, 1957.

Attempts to demonstrate, in vitro, specific antibodies in serum of allergic individuals have not been conclusive. In this study it was shown that antibody-like factors are present in the sera of treated and untreated ragweed-sensitive individuals. The highly sensitive hemagglutination technique of Stavitsky and Arquilla was used in these experiments. With rabbit erythrocytes sensitized with ragweed the hemagglutination reaction was positive in dilutions up to 1,024 in 4 sera of treated and 12 sera of untreated ragweed-sensitive individuals. Negative results were obtained in 30 normal human sera. The reactions were specific for ragweed and negative with other antigens such as grass pollen, wormwood, and bovine serum albumin. When sera that contained reagins were heated at 56 degrees for 11 hours, there was no change in their hemagglutination titer, but their ability to sensitize the skin was lost. The hemagglutination tests were positive only in those sera that demonstrated skin-sensitizing activity. This is not interpreted as evidence that the hemagglutination factor and the skin-sensitizing antibody are identical. The authors conclude that sera of individuals who are allergic to ragweed contain antibody-like factors which can be demonstrated in vitro. This system seems to be similar to other antigen-antibody systems. These antibodies are probably present only in very small concentrations, which explains why they have been difficult to detect. S. Stousland.

Asthma Caused by Parietaria in France. Panzani, P.: Presse méd. **64**: 908, 1956.

Parietaria officinalis, of the Urticaceae family, is a plant which grows abundantly on old walls and around houses in southern France. Its pollen fulfills Thommen's postulates as a cause of pollinosis. It pollinates from April to September and occasionally into the beginning of October. The pollen granules are 15 microns in diameter.

Twelve adult patients suffering from seasonal hay fever and severe asthma caused by this pollen were studied. All were born in southern France or lived there for many years. They exhibited marked positive skin reactions to Parietaria pollen extracts. Six of them reacted to extracts of other pollen. Preseasonal specific hyposensitization gave satisfactory results but was less effective than is usually obtained in other pollen sensitivities. More than 100 pollinosis patients from other parts of France were tested and failed to react to Parietaria pollen extract. Among several hundred children tested, including some who were allergic to grass and plantain pollens, not a single positive reaction to Parietaria pollen was observed. I. G.

Blood-Letting in Asthma. Blamoutier, P., and Blamoutier, J.: Presse méd. **64**: 1046, 1956.

The authors point out the beneficial effects of repeated minor blood-lettings in nonallergic, cyanotic, or plethoric asthmatic subjects, or in asthmatic women during the premenstrual or menopausal periods. In patients with protracted or repeated attacks of asthma the effect of rapidly withdrawing 250 c.c. to 400 c.c. of blood is spectacular. It may complement or substitute for steroid treatment. Blood-letting is particularly indicated in allergic coryza, asthma, hay fever, and the asthmatic bronchitis of childhood. These observations are based on the authors' experience of 900 bleedings in allergic asthmatics. The effect is probably due to a central analeptic respiratory action, a reduction of hypertension in the lesser circulation, a reflex action on bronchospasm and bronchial secretion, and stimulation of the pituitary adrenal axis as demonstrated by the Thorn test and changes in ascorbic acid content of the adrenals after experimental blood-letting in rats. I. G.

Evaluation of Therapeutic Results by Means of the "Protection Test" in 100 Cases of Various Forms of Asthma. Benda, R., Miravet, L. F., and Gartenlamb, G.: Presse méd. **64**: 2237, 1956.

The authors divided human sera according to their antihistamine properties as measured by their protective effects when injected into guinea pigs exposed to histamine aerosolization. Not all of the sera obtained from individuals considered normal (in contrast to asthmatics) had high "protecting properties" (expressed as coefficient "P"). Among the individuals studied, there were only about 10 per cent ("privileged") whose serum was entirely protective. The "P" of 100 patients with different forms of asthma was measured. Sixty-four of these sera had very little or no "protecting" properties; in the remainder, this property was markedly reduced. All of these asthmatics were treated with "protecting sera" and/or hormones, particularly delta-cortisone. In 59 cases there was clinical improvement and an increase in "P"; in 20 cases there was no clinical improvement or serum change; the rest showed varied responses.

The sera of 26 asthmatic patients were tested as to their "captation property" (the ability to reduce the biologic activity of a histamine solution on the isolated intestine strip of guinea pig). Only 4 sera possessed "captation properties"; the other 22 failed to show these properties regardless of their coefficient protection. After treatment, captation appeared in 11 cases in whom it was previously absent and paralleled an increase in "P." Captation was always accompanied by protection, while even the most elevated "P" could develop without any associated captation ability. It seemed that "protective" serum alone or associated with cortisone derivatives could modify "P" more easily than hormonal treatment alone. The "captation test" proved less reliable and less rapid in its responses as compared to the "protective test." I. G.

Dermatology

Advantages of Combining Hydrocortisone and Oxytetracycline Topically. Cornbleet, T., Barsky, S., and Hoit, L.: J. Invest. Dermat. **27**: 61, 1956.

Fifty patients with various dermatoses, including impetiginized atopic eczema, secondarily infected dermatitis venenata, and seborrheic dermatitis, were treated topically with 1 per cent hydrocortisone, 3 per cent oxytetracycline, or with a combination of both drugs. By controlled comparison tests,

it was found that in a majority of instances the lesions showed a greater improvement when the drugs were used in combination than when either was used alone. There was no instance in which the action of either drug was impaired when used in combination. The combination of an antibiotic with a topical steroid is regarded as good therapy in preventing the spread of overt or hidden infection in a lesion. M. C.

Contact Dermatitis With Spongiosis and Intraepidermal Vesiculation in the Acanthotic Skin of Guinea Pigs. Baer, R. L., Rosenthal, S. A., and Sims, C.: J. Invest. Dermat. **27**: 249, 1956.

Thirteen guinea pigs were sensitized to picryl chloride by the method of Chase or to 2,4 dinitrochlorobenzene by repeated intracutaneous injection. An area on each flank was clipped and painted with an acanthogenic agent such as squalene, Span 20, or sodium lauryl sulfate which produces thickening of the prickle cell layer. The acanthogenic agent was applied daily for 7 to 13 days with 2 two-day rest periods. From two to seven days after the last application, the acanthogenic-treated and control sites were tested by applications of the allergenic material and of the vehicle alone. Sites were examined 24 hours after these applications and punch biopsies were taken. There were no vesicles or bullae grossly visible, but the reactions were generally more intense at acanthotic sites than at untreated sites tested with the same allergen. Histologic examination showed eczematous changes in acanthotic-treated tissue tested with allergen in 9 of 13 guinea pigs. The epidermis showed irregular acanthosis of moderate to marked degree, intercellular edema, exocytosis, exoserosis, spongiosis, disturbance of the basal cell layer, and, in 3 specimens from different guinea pigs, vesicle formation.

These results indicated that the production of acanthosis in guinea pig skin rendered it capable of responding to contact allergens with intraepidermal changes similar to human contact-type allergic eczematous dermatitis. Normally the allergic guinea pig skin response to contact allergens is nonvesicular. Hence, the relative thickness of the prickle cell layer in the normal skin of guinea pigs may account for the failure of their skin to respond with charactertistic eczematous vesiculation. From these experiments, it appeared that the abnormal thickening of the prickle cell layer in human skin might possibly contribute to the genesis of eczematous dermatitis. M. C.

Eczema of the Eyelids. Theodore, F. H.: Ann. Allergy **14**: 484, 1956.

Eczema of the eyelids may be divided into three types: (1) contact allergy; (2) bacterial and fungal infections of the lid margins; and (3) a general group composed of atopic dermatitis, neurodermatitis, seborrheic dermatitis, and psoriasis.

Contact allergy is the most common cause of eyelid eczema, and cosmetics and ophthalmic drugs are the most frequent etiological agents. Cosmetic dermatitis usually begins with involvement of the upper lid at the medial portion, and is not accompanied by inflammation of the conjunctiva or eosinophilia. Diagnostic tests should be performed by applying the suspected materials in the manner in which they are normally encountered rather than by means of a closed patch test. Reactions to ophthalmic drugs begin with an inflammation of the conjunctiva and subsequently involve the adjacent skin. Itching and eosinophilia are present. The earliest signs of eczema due to eye drops may appear at the canthi and lower lids, whereas ointments first produce their reactions at the lid margins. Steroids, used locally or systemically, are the best form of therapy in contact allergy of the lids.

Infectious eczematoid dermatitis of the lids is usually caused by a staphylococcal infection, although occasionally streptococci or fungi may be the causal agents. The infection is usually primary about the eyes but it may be secondary to other skin pathology. Since it is impossible to distinguish between contact and staphylococcal eczema on the basis of the character of the dermatitis, it is necessary to demonstrate that the focal point of the process is not the skin about the eye but, rather, the eye itself or its adnexae. Important consideration in the differential diagnosis between staphylococcal and allergic types of eyelid eczema are discussed. A dual mechanism involving toxic and allergic components appears to be responsible for staphylococcal eczema. Intracutaneous tests with staph toxin or toxoid are of diagnostic value only when they induce marked reactions.

Treatment of staphylococcal eczema consists of local antibacterial applications and the use of antibiotics. Steroid ointments, toxoids, and vaccines may be of some help.

Nonspecific types of eyelid eczema may accompany generalized dermatoses, such as atopic dermatitis and neurodermatitis. The atopic type usually responds to steroid therapy. The other types of nonspecific involvement are best treated symptomatically. H. F.

Ultraviolet Light Factor in Chlorpromazine Dermatitis. Cahn, M. M., and Levy, E. J.: Arch. Dermat. **75**: 38, 1957.

Of 10 patients receiving chlorpromazine therapy, 5 developed an erythematous papular eruption on the exposed parts of the body during the summer. These patients were receiving no other medication. Liver function tests, both prior to and following the eruptions, were normal. The pruritus usually subsided in about 2 hours and the rash disappeared in about 24 hours following the exposure to sunlight. None of these individuals had difficulty tolerating winter sunlight and, if the drug was stopped several months in advance of the warm weather, they appeared to tolerate the summer sunlight as well.

Additional studies were made to determine the nature of the light factor which caused the eruption. Ten patients receiving chlorpromazine (including the 5 with the photosensitivity) and 5 normal subjects were exposed to the rays of a hot quartz mercury arc lamp on sites 2 cm. square on the upper back. No significant differences were noted among the 15 patients studied in the amount of ultraviolet required to produce minimal erythema. The ultraviolet rays between 3025A and 2968A were suspected of being responsible for the rash. The failure of the quartz lamp to precipitate undue reactions in the patients with chlorpromazine photosensitivity was attributed to a low concentration of these wave lengths in the quartz lamp rays. It is suggested that patients who develop chlorpromazine dermatitis need not be taken off chlorpromazine, since these eruptions are transitory and occur only in the height of the summer. Patients receiving the drug, however, should be advised to avoid undue exposure to the intense summer sunlight. R. W.

Miscellaneous Allergies

Penicillin Reaction Rates in Relation to Penicillin Usage in the Navy. Babione, R. W.: Antibiotic Med. & Clin. Ther. **6**: 388, 1956.

In the United States Navy and Marine Corps, allergic reactions to antibiotics which were serious enough to result in a loss of working time declined from 2,114 in 1951 to 861 in 1955, a reduction of 59 per cent in four years.

Penicillin was the offending agent in 97 per cent of the cases from 1953 to 1955. The diminution in reactions almost exactly paralleled the decrease in the rate of issue of injectable penicillin, but there was no such demonstrable relationship in regard to oral penicillin, of which the issue rate had increased since 1952. It was estimated that reactions occurred at the rate of 1.8 per billion units of injectable penicillin as used in the Navy. Each reaction included in these statistics was serious enough to incapacitate a man for more than 24 hours. Reactions of short duration, including some serious anaphylactic ones, were probably not included in this study. There were no deaths between 1951 and 1954, but 2 occurred in 1955 following the intramuscular administration of penicillin. M. C.

Allergic Reaction to Meprobamate. Report of a Case. Falk, M. S.: Arch. Dermat. **75**: 437, 1957.

Following a bout of acute alcoholism, a 29-year-old woman was given meprobamate (Equanil) in 400 mg. doses. After having taken 3 or 4 tablets, she developed a systemic reaction consisting of purpura, nausea, vomiting, and headache. She was admitted to the hospital with a temperature of 102° F., a blood pressure of 96/60, and a rapid pulse. The skin lesions were mainly in the intertriginous areas. The white blood count was elevated with 93 per cent polys and 4 per cent eosinophils. The bleeding and clotting times were normal. The Rumpel-Leede test was positive. The patient responded quickly to the administration of steroids and antihistamines and was discharged on the fourth day following her admission. Two months later she accidentally took another tablet of meprobamate. She developed a reaction similar to the previous one and had to be hospitalized again. This patient was given reserpine and tolerated it well. R. W.

Red Cell Abnormality and Autoimmune Antibody in Periodic Disease. De-Vries, A., Dannon, D., Nelken, D., and Henig, E.: Harefuah **52**: 1, 1957.

Twelve patients suffering from recurrent attacks of periodic diseases (also known as periodic or paroxysmal peritonitis or familial Mediterranean fever) were studied. Small dark red cells were found in the peripheral blood smears of all the patients. During the attack, these spherocytes were more typical and abundant than during the intervals. Ghosts of red cells were prepared by dialysis in a medium of which the osmotic pressure was gradually decreased. When examined by the electron microscope, these ghosts demonstrated a thinner and a smoother surface than the granular surface of normal ghosts. The serum of 7 patients contained antibodies which agglutinated normal erythrocytes of group O previously treated with papain. The agglutinin was not a hemolysin, was of the gamma globulin type, was not destroyed when incubated for 30 minutes at 56° C., was equally active at 6° and 37° C., and remained active for 6 months at minus 20° C.

All patients except one showed mild to severe degrees of anemia but no signs of hemolysis. In one patient, there was a rapid decrease of hemoglobin during the attack. In another a marked deposit of hemosiderin was noted in the spleen. A few of the healthy relatives of the patients also had at least one of the abnormal blood findings described. The authors suggest that periodic disease is caused by an autoimmune mechanism which develops on the basis of a constitutional abnormality manifested by defective structure of red cells. This would explain occasional associated allergic phenomena and the

familial and ethnic character of the disease. The possibility that there may be a common antigenicity of tissue cells (serous membranes) and red blood cells is suggested. I. G.

Anaphylaxis

A Quantitative Study of the Passive Arthus Reaction in the Rabbit Eye. Waksman, B. H., and Bullington, S. J.: J. Immunol. **76**: 441, 1956.

Typical Arthus reactions were induced in the rabbit uveal tract by simultaneous injection of antigen into the anterior chamber or the vitreous body and intravenous injection of homologous rabbit antibody (direct passive Arthus technique). Similar reactions were induced by the local injection of antibody and the intravenous injection of the corresponding antigen (reversed passive Arthus technique). The antigen-antibody systems employed involved egg albumin and bovine gamma globulin and the corresponding rabbit antisera, as well as purified diphtheria toxoid and corresponding horse antibody.

When either the direct or the reversed technique was employed, characteristic reactions appeared within one-half to 2 hours and reached their peak at 6 to 24 hours. The reaction was an acute fibrinous, hemorrhagic uveitis. The most significant findings were congestion of the iris vessels, edema of the iris with petechial hemorrhages, and an exudate or precipitate in the anterior chamber. Microscopically, the reaction developed most intensely in the ciliary body and to a lesser extent in the iris and choroid. The blood vessels were surrounded by edema fluid, massive exudates of polymorphonuclear leukocytes, and hemorrhage. It is significant that the areas most involved in the reaction, with the exception of the choroid, were those sites most intimately associated with the transfer of electrolytes and nonelectrolytes into and out of the eye. The reactions were similar when the intraocular injection was made either into the anterior chamber or into the vitreous body. This was attributed to the fact that substances introduced into the vitreous readily diffuse to the ciliary body and the anterior chamber.

When the local injection of antigen or antibody was made subconjunctivally and the other reactant was given intravenously, an Arthus reaction developed which was grossly and histologically indistinguishable from the type seen in the skin.

Similar experiments were carried out in a small number of guinea pigs. Neither an Arthus reaction nor a wheal and flare type of response could be produced by the direct or reversed techniques, regardless of the dose of antibody given, the site of local injection, or the interval between injections. B. S.

Experimental Allergy of Veins. Houcke, E., Merlen, J. F., and Chevat, H.: Presse méd. **64**: 1661, 1956.

Oxen were injected with a sensitizing dose of ovalbumin into the jugular vein. They were slaughtered 15 days later and the jugular vein was put in a myograph suspended in Tyrode's solution. When a shocking dose of ovalbumin was added to the bath or injected into the wall of the vein, the contractions became very irregular. Immediate histologic examination of the veins revealed edema of the wall, turgescence and vitrifaction of the collagen substance, multiplication of vasa vasorum, and prolification of histocytes and tissue eosinophiles. In control experiments using common commercial sclerosing agents of veins instead of antigen, no such effects were observed. The

normal contractions of veins were not changed by the addition of Adrenalin, histamine, or a mixture of histamine and Phenergan to the Tyrode's solution.
I. G.

Pharmacology, Physiology, and Pathology

The Antigenicity of Polyvinyl Pyrrolidone. Maurer, P. H.: J. Immunol. **77**: 105, 1956.

Polyvinyl pyrrolidone (PVP) preparations of different K values were injected intramuscularly in various doses into human volunteers. Blood specimens were drawn before and after the immunization procedure. Sera were assayed for antibody nitrogen by a quantitative precipitin method. The only sera which contained antibodies to PVP were those obtained from volunteers who had been immunized with the K-87 PVP. Two of the individuals developed systemic reactions following injection with this preparation. The immunologic response to K-87 PVP was found to be irregular, and the persistence of antibody varied considerably.

The sera obtained from individuals injected with PVP of lower K values contained no antibodies to these agents or to K-87 PVP. However, with sera containing K-87 PVP antibodies, a slight amount of precipitation could be demonstrated with K-62 and K-44 PVP, but not with K-30 or K-16 PVP. The cross reactions of these PVP preparations with anti-PVP K-87 sera were thought to be due to PVP molecules having similar structural groupings rather than to the presence of traces of K-87 in the other PVP preparations.

The material precipitated from the sera following addition of PVP K-87 was felt to be specific antibody to PVP because it was soluble only in excess PVP or N-vinyl pyrrolidone. PVP had no effect on the solubility of other antigen-antibody precipitates.

Rabbits were immunized with PVP K-30 or PVP K-87 either in a saline solution, as an alum precipitate, or in a water-in-oil adjuvant mixture. Antibody could not be detected in any of the rabbit sera, regardless of the method of immunization employed.

These studies demonstrate that PVP of very high molecular weight (K-87) is antigenic in man, but these findings have little bearing on the antigenicity of PVP K-30, which is the type presently under investigation as a suitable plasma expander.
B. S.

Studies on the Role of Histamine in the Increased Susceptibility to Bacterial Endotoxins Induced by Pertussis Vaccine. Abernathy, R. S., and Spink, W. W.: J. Immunol. **77**: 418, 1956.

Female mice of the Swiss-Webster and the ABC strains were used in these experiments. The Swiss-Webster was found to be the more histamine-resistant. After injections of pertussis vaccine, however, these animals became highly susceptible to histamine, while the animals of the ABC strain did not show any change.

Brucella endotoxin or heat-killed *B. abortus* or active infection with *B. melitensis* did not alter the reaction to histamine in either strain. After pertussis vaccination there was an increased lethality to brucella and typhoid endotoxin in both strains in contrast to the susceptibility to histamine, which was different in the two strains. The mode of death due to endotoxin was not affected in the mice treated with pertussis vaccine.

It had been suggested that endotoxin may have a histamine-releasing action. The action of the histamine-releasing agent 48/80 was compared in both

normal and pertussis-sensitized animals. No remarkable difference was found between the two groups. Adrenocorticosteroids and chlorpromazine protected nonsensitized Swiss-Webster mice against lethal amounts of brucella endotoxin, but Benadryl did not. In sensitized mice, however, chlorpromazine offered no protection, while the protective effects of corticosteroids and antihistamines were unchanged. Both normal and sensitized ABC mice tested with chlorpromazine against brucella endotoxin gave the same results as the Swiss-Webster mice. These findings suggest that histamine is not necessarily the mediator of susceptibility to endotoxin in pertussis-sensitized animals.

S. Stousland.

Studies on the Allergic Terrain. An Attempt at Treatment With Normal Human Serum. Parrot, J. L., and Laborde, C.: Presse méd. **64**: 1765, 1956.

It had been demonstrated previously that serum of normal individuals was capable of retaining in vitro part of the histamine added to it. This "histaminic potency" was not present in the serum of patients with allergic manifestations, such as asthma, urticaria, angioedema, eczema, migraine, gastro-duodenal ulcers, acute rheumatic fever, evolutive chronic polyarthritis, and tuberculosis with exudative manifestations or strongly positive skin reactions. This humoral difference was not related to allergenic specificity but was a characteristic of the "allergic terrain."

Twenty-seven allergic patients suffering from asthma (8), urticaria (8), migraine (5), eczema (4), or peptic ulcers (2) who failed to respond to the usual types of treatment were injected subcutaneously with normal serum having normal histaminopexic potency. Twenty-three patients were completely relieved within 2 or 3 weeks, 2 improved, and 2 failed to improve. The remission of symptoms lasted at least 4 months and in some cases over 3 years. The serum of the treated patients gradually acquired histaminopexic potency; the plasma histamine levels which had been abnormally high were lowered, and the capillary resistance which had been abnormally low was increased. This acquired histaminopexic potency disappeared when the serum was heated to 56° C. for 15 minutes. This acquired potency provided an objective guide for the need of further treatment. I. G.

Changes in Plasma Levels of 17-Hydroxycorticosteroids During the Intravenous Administration of ACTH. I. A Test of Adrenocortical Capacity in the Human. Eik-Nes, K., Sandberg, A. A., Nelson, D. H., Tyler, F. H., and Samuels, L. T.: J. Clin. Invest. **33**: 1502, 1954.

Thirty-nine normal subjects and six with adrenal insufficiency were given ACTH intravenously while in a fasting state. Plasma 17-hydroxycorticosteroids were determined at intervals. Maximal adrenal stimulation was obtained with a dose of from 15 to 25 I.U. of ACTH, and the optimal infusion time was 6 hours. The blood level after an 8-hour infusion was not significantly different from that at 6 hours. Little or no rise in plasma 17-hydroxycorticosteroids occurred in individuals with known adrenal insufficiency. This test by-passes certain factors which complicate the eosinophil reduction test and the test for urinary 17-ketosteroids. E. K.

Immunology

Precipitin Production in Chickens. XIII. A Quantitative Study of the Effect of Simultaneous Injection of Two Antigens. Abramoff, P., and Wolfe, H. R.: J. Immunol. **77**: 94, 1956.

Chickens were injected intravenously with bovine serum albumin and human gamma globulin, given simultaneously. In the control groups, only one of the antigens was given. Antibody nitrogen determinations were made on serum specimens drawn 8 days following antigenic stimulation. When the dose of antigen was 10 mg. per kilogram of body weight, the antibody responses in the experimental group were considerably less than those obtained in the control group. When the dose was increased to 20 mg. per kilogram of body weight, the antibody responses in the experimental animals at the eighth day were markedly diminished to bovine serum albumin and only slightly reduced to human gamma globulin in comparison to the responses obtained in the control animals. This experiment was repeated with bleedings done at intervals varying from 4 to 18 days following antigenic stimulation. In the control groups, the average antibody responses to the two antigens were approximately equivalent at their peaks. However, the peak of antibody response occurred 2 days earlier with human gamma globulin than with bovine serum albumin. Following the peak, the decrease in antibody titers was slower with human gamma globulin than with bovine serum albumin. The antibody response to human gamma globulin in the experimental group was approximately equivalent to that of the controls. In the experimental group, the human gamma globulin titers decreased rapidly while the antibodies to bovine serum albumin were increasing. In this group, the response to bovine serum albumin was only about 50 per cent that of the controls. The peak of response was reached about 10 days after the antigen injection in the experimental animals and 8 days after injection in the control animals. This "crowding out" of anti-albumin antibodies may result from prior utilization by the gamma globulin of many of the reactive sites leaving fewer sites for production of anti-albumin antibodies. This ability of gamma globulin to crowd out albumin may be due to the larger molecular weight of the globulin.

In another study, bovine hemoglobin and bovine albumin were injected simultaneously into experimental groups of chickens and singly into control groups. Blood taken on the eighth day revealed a reduced antibody titer for bovine albumin in the experimental group as compared to that in the controls. Antibodies could not be demonstrated against bovine hemoglobin in either group. The authors suggest that bovine hemoglobin, although incapable of producing detectable antibody, may be able to bind reactive sites in the antibody-producing mechanism and thus exercise a crowding-out effect on the production of anti-albumin antibodies. B. S.

A Study of Antigenic Relationships Between Trichinella Spiralis and Salmonella Typhi. Weiner, L. M., and Price, S.: J. Immunol. **77**: 111, 1956.

Rabbits were immunized with *T. spiralis* or *S. typhi* and high-titered antisera were produced. Preimmunization serum samples from these experimental rabbits contained no antibodies for either antigen. The trichinella antiserum was found to contain agglutinins for typhoid "O" and "H" antigens. The typhoid antiserum contained precipitin antibodies for trichinella larval antigen. One absorption of the trichinella antiserum with a growth of *S. typhi* removed all typhoid agglutinins and resulted in a threefold reduction in the trichinella precipitin titer. The absorption of antityphoid serum with dried ground trichinella larvae produced a loss of all trichinella antibody and a sharp reduction of "O" antibody titer, while the "H" titer remained relatively unchanged. These findings indicate that a cross-antigenicity exists between *T. spiralis* and *S. typhi.*

The ability of trichinella antiserum to react with other bacterial antigens was further investigated. This antiserum was found to react with *Salmonella paratyphi* A, B, and C, and with *Klebsiella pneumoniae,* but not with *Shigella alkalescens.* The reactions with the paratyphoid species were probably due to antigenic components which they have in common with *S. typhi.* The positive reaction with *Kl. pneumoniae* cannot be explained on the basis of any known antigenic relationships and may indicate a relationship between this organism and still another trichinella larval component.

Serum samples from various patients and normal volunteers were studied. The reliability of these data was considered questionable since control serum specimens and adequate histories were not always available. One patient with proved trichinosis, who had no history of typhoid fever or immunizations, showed serum antibodies to trichinella and to typhoid "O" and "H" antigens. In another patient with clinical typhoid fever and no history or symptoms referable to trichinosis, antibodies were also found to both antigens. On the other hand, a volunteer who had recently received T.A.B. immunizations had typhoid antibodies but no trichinella antibodies. B. S.

A Study of the Sensitivity of Human Leukocytes to Tuberculin and Other Bacterial Products by the Blatt, Nantz, and Rehm Technique. Scherago, M., Partin, J. C., and Hall, H. E.: Ann. Allergy **15**: 1, 1957.

The Blatt, Nantz, Rehm test for sensitivity of human leukocytes to bacterial products was compared with the Hall and Scherago tissue culture technique which differentiated by cytotoxic effect between the leukocytes of tuberculous and nontuberculous individuals. In the BNR test, the morphology of the sensitized leukocytes is altered when they are brought in contact with bacterial filtrates. The Hall and Scherago technique for tissue culture is dependent upon the inhibition of leukocytic migration by the test materials. Since the BNR technique is supposed to give informative results in the tuberculin type of hypersensitivity, the two techniques were compared, using leukocytes obtained from 25 patients with active tuberculosis. Twenty-two (88 per cent) of the 25 samples gave positive reactions with the tissue culture technique of Hall and Scherago, while only 4 (16 per cent) were found to be sensitive with the BNR technique. Of 28 nontuberculous and inactive tuberculous individuals, only 3 (10 per cent) gave positive leukocytic reactions to tuberculin by the tissue culture technique, and these were cases with inactive tuberculosis. With the BNR technique, the leukocytes of 5 (18 per cent) of the nontuberculous individuals gave positive reactions. None of these had ever had any evidence of tuberculosis.

Further experiments were done with culture filtrates of staphylococci, streptococci, pneumococci, and other organisms. No significant differences were noted with the BNR technique between the reactions obtained with the leukocytes from 47 allergic individuals who had given positive skin reactions to bacterial filtrates and those obtained with the leukocytes from appropriate controls. It was also determined that there was no appreciable difference in the susceptibility to lysis when the leukocytes from tuberculous and nontuberculous individuals were incubated with OT. In another experiment it was shown that leukocytes failed to remain viable after exposure to the BNR reagent for 18 hours. This is contrary to the claim of Blatt that leukocytes remain viable for 36 hours. From these findings, it is concluded that the BNR technique is not a reliable method of testing for bacterial allergy. H. F.

Delayed Hypersensitivity. I. Induction of Hypersensitivity to Diphtheria Toxin in Guinea Pigs by Infection With Corynebacterium Diphtheriae. Uhr, J. W., Pappenheimer, A. M., Jr., and Yoneda, M.: J. Exper. Med. **105**: 1, 1957.

Delayed cutaneous tuberculin-type hypersensitivity was induced in guinea pigs by the intracutaneous injection of live toxigenic diphtheria bacilli. The animals were protected with horse antitoxin administered either before or after the infection. The horse antitoxin was rapidly removed from the circulation because of its high antigenicity. Active antitoxic antibody formation was inhibited and the animals remained Schick-positive when tested from 2 to 3 weeks after infection. The type of delayed sensitivity induced was studied by the intraperitoneal injection of lymph node cells from sensitized animals into normal guinea pigs. The recipients were sensitized thereby and showed delayed cutaneous reactions to purified diphtheria toxoid. E. K.

Delayed Hypersensitivity. II. Induction of Hypersensitivity in Guinea Pigs by Means of Antigen-Antibody Complexes. Uhr, J. W., Salvin, S. B., and Pappenheimer, A. M., Jr.: J. Exper. Med. **105**: 11, 1957.

Delayed cutaneous tuberculin type hypersensitivity was induced by the injection of antigen-antibody complexes in an adjuvant mixture into guinea pig foot pads. Diphtheria toxoid and ovalbumin were the antigens employed. The complexes were formed in the region of antibody excess. The degree of hypersensitivity attained was as great as or greater than that induced by infection. Little or no circulating antibody could be found from 2 or 3 weeks after sensitization.

The presence of mycobacteria in the adjuvant mixture enhanced the production of delayed hypersensitivity sensitization by other routes, such as the subcutaneous, intramuscular, intraperitoneal, or intravenous. Without mycobacteria, sensitization could be accomplished by the intracutaneous route only. When antitoxin was given intraperitoneally 24 hours prior to the intracutaneous injection of diphtheria toxoid in oil and water emulsion, pronounced delayed cutaneous hypersensitivity was demonstrable on challenge 2 weeks later. Antitoxin derived from horse, human, or guinea pig sources worked equally well in this experiment. The combination of toxoid with an excess of nonprecipitating skin-sensitizing human antitoxin also induced the delayed hypersensitive state. Delayed skin reactions could be elicited as early as the third or fourth day following sensitization with toxoid-antitoxin complex in incomplete adjuvant.

The sensitization of guinea pigs with free toxoid antigen or complexes formed in the region of antigen excess resulted in both immediate and delayed forms of hypersensitivity. Arthus reactions were observed in the course of some of these experiments but they required the presence of circulating antibody. They appeared earlier than the tuberculin type of reaction and usually were fading rapidly at 24 hours when tuberculin type reactions were maximal.

Only 1 or 2 micrograms of protein antigens, combined with antibody and injected intracutaneously, was sufficient to produce maximal tuberculin type delayed cutaneous sensitivity in guinea pigs, without circulating antibody formation. When large conventional doses (a milligram or more) of protein were used, high circulating antibody levels resulted and the reactions observed were complex. E. K.

The Nature of the Immunologic Inadequacy of Neonatal Rabbits as Revealed by Cell Transfer Studies. Dixon, F. J., and Weigle, W. O.: J. Exper. Med. **105**: 75, 1957.

Cells from lymph nodes in the process of active antibody formation were removed from rabbits sensitized with bovine serum albumin, gamma globulin, or a soluble extract of *Shigella paradysenteriae*. These cells were injected into 5- or 6-day-old rabbits and into irradiated and normal adult rabbits. Antigen labeled with I^{131} was administered intramuscularly or intravenously either a few hours before or at the time of cell transfer. The level of the labeled antigen served as an indicator of antibody production. Agglutination titers for bacterial antigen were also followed. No immune response was detected in any of the neonatal recipients when either normal or previously immunized cells were injected. Adult rabbits reacted in the usual manner, both normal and irradiated adults showing antibody formation after receiving the transfused donor lymph node cells. Histologic study showed the survival of transferred cells in neonatal recipients to be comparable to that in adults, but plasma cells did not develop in the transfer sites in neonatal recipients as they did in adults. Moreover, in adults the transplanted cells at the periphery of the deposits tended to accumulate around nerves and blood vessels. Such orientation occurred later in neonatal rabbits in whom there did not appear to be a comparable degree of post cellular reaction. The poor immune responses of the neonatal rabbits were not necessarily caused by a lack of suitable antibody-forming cells, but may have been due to the absence of a supporting environment suitable for competent cells when they were supplied.

E. K.

The Influence of Adrenocorticotropic and Growth Hormones on Antibody Formation. Hayshida, T., and Li, C. H.: J. Exper. Med. **105**: 93, 1957.

A purified fraction of *Pasteurella pestis* was used as an antigen in 3-month-old rats. When ACTH was administered in doses just sufficient to prevent growth, serum antibody levels in treated animals were depressed as compared with those in the control animals. Growth hormone, somatotropin (STH), when given alone, did not affect antibody production significantly although the animals gained weight rapidly. When STH was administered with ACTH the antibody depression produced by the latter was counteracted. It is suggested that the antibody depression induced by ACTH is the result of a decreased rate of protein synthesis.

E. K.

Duck-Embryo Rabies Vaccine. Study of Fixed Virus Vaccine Grown in Embryonated Duck Eggs and Killed With Beta-Propiolactone (BPL). Peck, F. B., Jr., Powell, H. M., and Culbertson, C. G.: J. A. M. A. **162**: 1373, 1956.

Rabies virus was grown in embryonated duck eggs and killed with beta-propriolactone (BPL). Concentrations of BPL up to 1:4,000 killed embryonated duck-egg-fixed virus without loss of antigenicity. Clinical response to the vaccine was studied in 32 nonallergic volunteers who, in most instances, received a series of 14 injections of vaccine. Detectable antibody appeared from 7 to 10 days after the first inoculation and was still present on the thirtieth day. No untoward reactions occurred, except in one subject who

developed fever and chills after the sixth injection of the series. It is recommended that the vaccine be used cautiously in allergic individuals. It is hoped that the absence of brain tissue in this vaccine will eliminate the neuroparalytic accidents which have been attributed to the presence of such nerve tissue in conventional antirabies vaccines. M. C.

Miscellaneous

The Use of a New Sustained-Release Antibacterial Agent in General Practice. Bishoff, R. J.: Antibiotic Med. & Clin. Ther. **6**: 399, 1956.

Sulfaethylthiadiazole (Sul-Spansion) in a sustained-release dosage form was given to 78 unselected patients with systemic infections. There were 74 patients with respiratory infections which included pharyngitis, tonsillitis, bronchitis, tracheobronchitis, bronchopneumonitis, otitis media, and chronic rhinitis, and 4 patients with cystitis. Bacterial cultures were made from the patient's ears, nose, throat, or urine. Sensitivity of the infecting organisms to 0.25 and 1.0 mg. concentrations of sulfaethylthiadiazole was determined by the disc method. Adult patients received 2.0 Gm. of the sustained-release suspension every 12 hours. Pediatric doses were computed on the basis of 0.32 Gm./15 lb. body weight/day and were also given at 12-hour intervals. In order to obtain rapid onset of antibacterial activity the initial dose was doubled. On this regimen, 76 patients were cured or greatly improved; 2 patients, one with acute tonsillitis and the other with acute pharyngitis, failed to respond to therapy. No side effects were observed during or after therapy. Of the 159 organisms isolated from the patients' specimens during the study, 143 or 90 per cent were sensitive to the 0.25 mg. concentration of sulfaethylthiadiazole. There was a high degree (98 per cent) of sensitivity of staphylococci to the drug and excellent clinical responses were obtained in patients with infections due to these organisms. Gram-negative and other gram-positive bacterial infections were also successfully treated with sulfaethylthiadiazole. It appeared from this study that this drug, in sustained-release dosage form, can be used successfully in treating minor infections without resorting to antibiotics, which may be reserved for more serious illnesses. M. C.

A Preliminary Report on Typhoid, Typhus, Tetanus, and Cholera Immunizations During Pregnancy. Freda, V. J.: Am. J. Obst. & Gynec. **71**: 1134, 1956.

The increased fetal mortality due to typhoid fever, tetanus, or cholera complicating pregnancy is well established, but little is known regarding complications of pregnancy incident to immunization against these diseases.

Initial immunizations were carried out with typhoid, typhus, tetanus, and cholera in 45 pregnant Japanese women in an American military hospital in Japan. Booster injections were administered to a second group of 62 pregnant women, military dependents, who had received their initial immunizations prior to overseas travel and prior to pregnancy. There were no instances of abortion immediately following any of the injections, nor could any complications of pregnancy be directly attributed to the injections. The incidence of complications of pregnancy in this group of 107 patients was not significantly different from that in a control group of pregnant women who did not receive immunization injections. J. S.

Mass Histamine Poisoning Due to Ingestion of Tuna Fish. Boyer, J., Depierre, F., Tissier, M., and Jacob, L.: Presse méd. **64**: 1003, 1956.

A mass food poisoning occurred in Paris on Aug. 31 and Sept. 7, 1955, which were very hot days. It was found to be caused by the ingestion of tuna fish which had been caught in the Mediterranean and shipped without proper refrigeration. Of 4,000 persons who ate the fish, 400 were affected. The food did not appear adulterated and poisoning occurred even when the fish had been well cooked. Symptoms appeared from 5 minutes to 3 hours after ingestion and consisted of malaise, vertigo, severe headache, palpitation, and faintness. Vasodilation phenomena of the face and neck and occasionally pruritus, urticaria, and angioedema were noted. Tachycardia and sometimes hypotension occurred. Within a few hours, the symptoms subsided. They were not relieved by aspirin or Adrenalin; antihistamines caused a rapid sedation. Some patients also developed epigastric pains, nausea, vomiting, and diarrhea about 2 hours after consumption of the food. These symptoms lasted one day.

Four samples of the fish which were tested for their histamine content by means of the isolated guinea pig intestinal strip revealed values of 28, 80, 100, and 690 mg. per kilogram. Five other samples contained 1.8 to 4.0 Gm. per kilogram (100 mg. per kilogram is considered above normal but nontoxic). The authors suggest that these larger quantities of histamine were most likely formed by microbial fermentation and decarboxylization of histidine which is abundant in the muscle and hemoglobin of tuna fish. Methods of prevention of histamine poisoning are discussed. I. G.